assert that the newly added claims 29-32 meet all criteria of patentability. In addition to the remarks provided below, the comments provided by Dr. Gauldie address and obviate all of the rejections of record.

Enablement issues

In the last office action, the Examiner rejected now cancelled claims 1-19 and 26-28 under 35 USC § 112, first paragraph, as containing subject matter that is not enabled by the specification. Applicants respectfully traverse, and believe that the new pending claims further avoid any questions concerning enablement, especially in view of the factual evidence provided in the Gauldie Declaration. To reiterate Applicants' previous comments, Applicants generally agree with the Examiner's position that the arts of gene therapy and genetic immunization can be unpredictable. However, Applicants assert that the teachings, disclosure and data contained in the subject application provided an enabling disclosure when combined with the general knowledge in the art. As Dr. Gauldie states in his declaration, more and more evidence in the relevant literature is coming to light, including the specific evidence provided in the Gauldie Declaration, that proves the data in the subject application, and the scientific assertions in the application, are true and accurate. That is, advenoviral vectors expressing a targeted antigen that are adminstered to gastrointestinal or genitourinary cells effectuates a reproducible, successful protection against the underlying, targeted pathogen.

The attached Gauldie Declaration shows that administration of adenoviral vectors was successful at immunizing against targeted pathogens. First, Exhibit B of the Gauldie Declaration demonstrates that Adenoviral-based gene delivery in the lower GI tract induces antigen-specific immune responses and protection from Tumour challenge, correlating with the presence of CTL positive reactions in spleen cells from immunized animals. Exhibit C of the Gauldie Declaration demonstrates that Adenoviral based antigen gene delivery to rectal epithelium induces protective local immunity against HSV-2 infection, challenged either by vaginal or rectal administration of the pathogen. Accordingly, these studies provide *in vivo* confirmation to the assertions and scientific data contained in the subject application. "In view of these two studies, there can be no

question that the claimed methods, as claimed in Applicants' most recent response filed September 15, 2002 [sic], are directed to a useful, therapeutic vaccination methodology." See Gauldie Declaration, paragraph 2. Applicants respectfully request that claims 29-32 be found enabled under 35 USC § 112, first paragraph.

Prior art issues

In light of the confirmatory data provided in the attached Gauldie Declaration, there can be no question that the claimed methods represent a therapeutic vaccination approach. As such, the pending prior art rejections must fall. As the Examiner makes poignantly clear, "neither Wang nor Henning teach a working example of a therapeutic effect," (emphasis added) see page 15, paragraph 2 of the latest office action. As demonstrated from CTL assays provided in the subject application, and the confirmatory *in vivo* data, Applicants invention is directed to an undoubtedly therapeutic vaccination method. Under well-established tenets of patent law, Applicants pending claims should be found novel and nonobvious based on this grounds alone. The prior art does not teach or suggest all of the elements of the claimed invention, namely a vaccination method that is therapeutic.

Should the Patent Office have any concerns that the prior art inherently discloses the claimed invention, Applicants emphatically point out that inherency requires a realization or possession of the underlying invention. Furthermore, like anticipation, inherency requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference. See the following summary of the law on inherency:

> To be patented an invention must be new. 35 U.S.C. §§101, 102(a), (e). If it is not new, that is, if it was known to others, it is said to be "anticipated." Hoover Group, Inc. v. Custom Metalcraft, Inc., 66 F.3d 299, 302, 36 USPQ2d 1101, 1103 (Fed. Cir. 1995) ("lack of novelty (often called 'anticipation') requires that the same invention, including each element and limitation of the claims, was known or used by others before it was invented by the patentee"). Anticipation is a question of fact, as is

> the question of inherency. In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). Its proof differs from that for obviousness, 35 U.S.C. §103, in that prior knowledge by others requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference (emphasis added). In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999); Constant v. Advanced Micro-Devices, Inc., 848 F.2d 1560, 1571, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). The single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention. Crown Operations International, Ltd. v. Solutia Inc., 289 F.3d 1367, 1375, 62 USPQ2d 1917, 1921 (Fed. Cir. 2002); In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it").

Dr. Gauldie's Declaration establishes that neither Henning nor Wang provide an enabling disclosure of a therapeutic vaccination method as to place the invention in the possession of the public. See Gauldie Declaration, paragraphs 3 and 4. Thus, prior to Applicants' teachings in the subject application, the public was not in possession of such a therapeutic method. In support of this assertion, Applicants provide the following excerpts from the Gauldie Declaration:

> "The Henning references disclose a method of introducing nucleic acid into the intestine using naked DNA or using various viral vectors. Henning discloses a few hypothetical examples of introducing DNA into intestinal cells. I point out that none of the examples discuss the use of an adenoviral vector; they are limited to retrovirus vectors, which are of limited use in vivo. Furthermore, Henning provides no working example, either in vitro or in vivo, of a methodology that may act immunize an animal. Based on the teachings of Henning, one skilled in the art is still left wondering whether cells can be transfected in the intestine *in vivo* to express a given gene. One skilled in the art knows no more about whether a gene can be reproducibly expressed in the intestine, much less whether an animal can be immunized against a specific pathogen by expression of a given gene. There is simply no connection between the method of exposing intestinal cells to a nucleic acid taught by Henning and successfully expressing a gene, whereby such expression leads to a successful vaccination of an animal against a given pathogen. The subject application is the first demonstration, as far

as I am aware, that shows successful introduction of a gene into genitourinary epithelial cells using an adenoviral vector, whereby a protein antigen is generated that induces an immune response." Gauldie Declaration, paragraph 3.

With respect to the Wang et al. reference, it discloses a specific study involving the exposure of vaginal mucosa to a non-viral vector expressing HIV-1 envelope proteins. The study shows that exposure to the non-viral based DNA plasmid produces immunoglobulins that showed activity in the in vitro cell-free infection assay. The assay involved taking vaginal washes from treated and non-treated animals and combining the wash with HIV-1/MN cell-free virus. The cell free virus was then combined with MT-2 cells, and the ability of the virus to infect the cells was observed. In some cases, it does appear that something in the vaginal wash affects the ability of the virus to infect the MT-2 cells. It is conjectured (emphasis added) by Wang et al. that it is immunoglobulins present in the vaginal wash that is affecting the ability of the cell-free virus to infect the MT-2 cells. This study provides little additional information over Henning as to whether a given viral vector is able to be introduced into mucosal cells, express a gene of interest, and induce a protective immune response against a given pathogen. There is the suggestion that it may be worthwhile to study different routes of administration using different vectors. However, in view of either Henning or Wang, it cannot be said that any given route of administration, using non viral or viral vectors, would vaccinate a treated animal with a reasonable expectation of success. The Applicants of the present application are the first to demonstrate that specific vaccination is achievable through gastrointestinal or genitourinary routes by application of an adenoviral vector encoding a specific antigen gene." Gauldie Declaration, paragraph 4.

The foregoing excerpts, and data, in the Gauldie Declaration leave little doubt that the Henning and Wang references fail to demonstrate a realization or possession of a therapeutic vaccination method. Therefore, neither Henning nor Wang, alone, or in combination, teach all of the elements of the claimed invention, either expressly or inherently.

Applicants assert that all pending claims are in condition for allowance, and such action is respectfully requested. Applicants request that the Examiner call the undersigned to arrange for a telephonic interview should the Examiner believe that any issues of patentability remain.

Respectfully submitted,

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